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Sensitive and direct determination of lithium by mixed-mode chromatography and charged aerosol detection

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ABSTRACT

A sensitive analytical method using mixed mode HPLC separation coupled with charged aerosol detection (CAD) was developed for quantitative analysis of lithium. The method is capable of separating lithium ion from different drug matrices and other ions in a single run thus eliminating the organic matrix and ionic analyte interferences without extensive sample preparation such as derivatization and extraction. The separation space and chromatographic conditions are defined by systematic studies of the retention behaviors of lithium and potential interfering ions and different type of pharmaceutical APIs (active pharmaceutical ingredients) under reversed-phase, HILIC and cation/anion exchange mechanisms. Compared to other current analytical techniques for lithium analysis, the presented method provides a new approach and demonstrates high sensitivity (0.02 ng for LOD and 0.08 ng for LOQ in both standard and sample solution). The method has been validated for pharmaceutical samples and can be potentially applied to biological, food and environmental samples.

1. Introduction

Lithium is an alkali metal and exists mainly as lithium salts in nature. Lithium and its compounds have wide industrial applications, including but not limited to pharmaceutical, material, automobile and batteries. Lithium carbonate is used as a prescription drug for treating mania and bipolar disorders. It has a narrow therapeutic index and the blood concentration of lithium is required to remain in a tight range of 2.8–8.3 mg/L [1–3]. Higher level could pose serious and even lethal toxicity to the patients, while lower levels do not provide adequate efficacy. It is very important to accurately quantitate blood lithium concentration to ensure drug efficacy and patients safety.

Lithium may occur in pharmaceutical products as a residual impurity due to lithium containing reagents often used in the process for drug synthesis. For example, lithium salt is a commonly used catalyst for pericyclic reactions [4] and asymmetric additions [5,6]. Organolithium compounds are reactive nucleophile reagents that are widely used for Li/H exchange and nucleophilic addition reactions to other carbon electrophiles [7]. The USP Ad Hoc Advisory Panel has proposed a limit of 6 μg/g for lithium in oral and parenteral materials [8], and ICH Q3D proposed a limit of 78 μg/g, 39 μg/g and 2.5 μg/g for lithium respectively in oral, parenteral and inhaled drugs [9]. Thus, it is critical to sensitively quantify trace amounts of lithium in pharmaceutical products to ensure patient safety.

Currently, there are various analytical techniques for lithium analysis including flame-AES [10,11], flame-AAS [12], ICP-AES [3,13], ICP-MS [14,15], spectrofluometry [16,17], flow through optode [18] and potentiometry with ion selective electrodes [19]. ICP spectroscopy is widely used for elemental analysis. The sensitivity for lithium is ideally at 100 ppb [3] by ICP-AES and 0.05 ppb [15] by ICP-MS. However, ICP spectroscopy methods are subject to matrix and spectral interferences for lithium analysis [10,20]. Spectral interference are caused by inter-elemental spectra overlapping, especially from sodium and potassium [12,15,21], and other elements or molecules such as calcium, magnesium, chloride, glucose, phosphate and ethanol [15,22,23]. The matrices of various drugs have been found to interfere with lithium analysis as well [10]. While sodium and potassium can strongly enhance the signal for lithium [12,21] chloride depresses the signal [23]. Spectral interference may be overcome by adding similar concentration of the interfering elements to the standard solution. However if the amount of interfering elements is not known in the samples, the approach is invalid. In ICP-MS, lithium ionization is affected by sodium, calcium and potassium which cause inaccurate analysis result [20].

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Ion-selective electrode (ISE) method is fast and sensitive, especially for clinical samples. However, ionic interference and selectivity is a major limitation. Additionally, the effect of ionic strength of sample solution and potential drift during a sequence measurement are frequently present. There have been efforts made to use aromatic organic reagents, crown ether and amide ionophores to achieve high lithium selectivity over sodium for blood lithium analysis [24]. For pharmaceutical analysis, method speed and sensitivity as well as method selectivity, robustness, transferability and the automation capability are very important. Due to the large amount of samples, it is desired to have automated sample analysis for pharmaceutics with unattended and non-interrupt sequence automation. Therefore, ISE is not considered a suitable method here for pharmaceutical samples whereas the methods are expected to be used in a regulated environment and transferred to different manufacturing and QC sites for large amount of samples.

Extraction of lithium from the matrix could help to reduce or eliminate the matrix effect and improves the analysis result. However, extensive sample preparations including complete sample digestion and solid–liquid extraction are needed. Often extraction is not pragmatic and sample recovery is problematic, particularly for trace level analysis.

Ion chromatography has been used for trace amount lithium analysis [22,25,26]. In ion chromatography, lithium is separated from sodium and potassium thus eliminating the elemental interference as encountered in spectroscopic techniques. However, ion chromatography requires aqueous mobile phase for separation and cannot tolerate the injection of large amount of drug with low solubility. Additionally, ion chromatography requires a special LC system and the detection is typically limited to conductivity and electrochemical detectors.

HILIC has been used for analysis of polar and charged analytes such as proteins and ions [27,28]. In HILIC mode, it is generally considered that water layer forms on the polar stationary phase. The polar analyte partitions into this water absorbed layer and gets retained, the less polar analyte has less penetration to the layer thus elutes earlier with the non-polar organic mobile phase. Since high organic mobile phase is needed to retain the polar compounds, by using HILIC retention mechanism alone is not enough for complex samples that contain components with distinct polarity, hydrophobicity and charge status.

The pharmaceutical API matrix includes acidic, basic and neutral small molecule compounds that have different physico-chemical properties and vary widely in retention time by chromatography. The interfering cations (Na^+, K^+) and anions (Cl^-, PO_4^{3-}) frequently exist in drug matrix. Due to the wide range of chemical properties from these potential interfering components, it is almost impossible to separate each analyte using a single stationary phase with a single retention mechanism. Often it requires different chromatography conditions for the assay due to variation of the matrix compounds which create repeated works in method development and validations. Mixed mode stationary phases that had characteristics of anion exchange chromatography (AEX) and hydrophobic interaction chromatography (HIC) were initially reported for protein separation [29]. In recent years, mixed mode columns have become a popular tool that is complimentary to conventional single phase columns. Mixed-mode HPLC coupled with CAD detection has proven to be an excellent approach for ion analysis [30]. In this study, we explored developing a mixed-mode analysis method to separate lithium cation from the major interfering ions and different matrices. The purpose is to build a sensitive and accurate platform method for lithium analysis for pharmaceutical products possessing different physicochemical properties, and eliminate organic matrix and inorganic ion interferences without sample preconcentration or derivatization.

2. Experimental

2.1. Reagents and materials

All chemicals were ACS grade or better unless otherwise indicated. Lithium hydroxide monohydrate was from BP Biomedicals (Solon, OH, USA). Sodium chloride, potassium phosphate and sodium naproxene were from Sigma–Aldrich (St. Louis, MO, USA). Tamoxifene was from MP Biomedicals (Solon, OH, USA). Drug compounds GB1, GB2, GN1 were synthesized at Genentech.

HPLC grade acetonitrile was from Burdick & Jackson (Morristown, NJ, USA) and ammonium formate from Sigma–Aldrich (St. Louis, MO, USA). De-ionized water (>18.2 MO) was from Milli-Q water purification system (Millipore, Bedford, MA, USA).

Ion free polypropylene HPLC vial with septa and cap (PN 079812) were from Thermo Fisher Scientific (Sunnyvale, CA, USA).

2.2. Instrumentation

The chromatographic system included an Agilent HP-1200 series high performance liquid chromatography (Agilent Technologies, Santa Clara, CA) equipped with an on-line degasser, quarternary pump, autosampler, column thermostat, diode array UV detector and a Corona Plus CAD detector (Thermo Fisher Scientific, Chelmsford, MA). ChemStation software version B.04.01 (Agilent Technologies, Santa Clara, CA) was used for data acquisition and processing.

Column used is Thermo Fisher Scientific's Acclaim Trinity P1 (3.0 mm × 50 mm, 3 μm, PN 071388).

2.3. Chromatographic conditions

For a ternary mixed phase separation, three mobile phase components were used: 50 mM or 100 mM ammonium formate buffer (pH 4.0), de-ionized water and acetonitrile. Gradient elution was used for separation of lithium from the interfering ions and drug matrix. The flow rate was 0.5 mL/min. The injection volume was 10 μL. CAD detection operated under a nitrogen pressure of 35 psi.

In the subsequent chromatographic calculation, void time (t^0) was determined by the elution time of an unretained solvent peak. The retention factor k' was calculated using the formula: $k' = (t^R - t^0)/t^0$, where t^R is the retention time of analyte peak. Limit of detection (LOD) is based on peak signal/noise ≥3 and Limit of Quantitation (LOQ) ≥10.

2.4. Standard and sample preparation

All standard and samples were prepared in diluent acetonitrile/water (1/1, v/v) and class A glass volumetric flask with sonication and vortex to facilitate dissolution. The solutions were transferred to ion free polypropylene HPLC vials for analysis.

3. Results and discussion

Separation of ions and small molecule drugs was tested using reversed-phase (C18, C4) and HILIC stationary phases. However, separation of all components using a single stationary phase was not possible with these columns. A mixed mode separation mechanism was investigated for a solution. Various mixed mode columns were evaluated for ion separation including Primesep AB, ZIC-pHILIC, Obelisc N and Acclaim Trinity P1. Among them, Acclaim Trinity P1 column showed superior selectivity in ion separation. The Acclaim Trinity P1 column is constructed of silica base modified with negatively charged polymer surface and positively charged inner-pore with covalently bonded organic layer. The silica surface provides HILIC and strong cation exchange interaction, the inner

pore provides reversed phase and weak anion exchange interaction [27]. This combination of RP/CEX/AEX would likely be efficient for the purpose of the study. Using HILIC mechanism, the more hydrophobic drug matrix could be eluted early or in the void, and lithium and the interfering ions could be retained longer then separated by ion exchange mechanism. In order to achieve the desired separation, we studied the HILIC/hydrophobic and ion exchange interactions on the retention of Li^+, Na^+, K^+, Cl^- and PO_4^{3-} ions and the matrix API compounds. Based on the behaviors of the ions and matrices, we developed a platform method for lithium analysis that eliminates the elemental and matrix interference.

3.1. HILIC/ion exchange characteristics in lithium/cation/anion separation

The retention factor k' of Li^+, Na^+, K^+ and Cl^- vs. acetonitrile levels were studied under ionic or HILIC conditions using fixed 5 mM ammonium formate (pH 4.0) in 10–95% of acetonitrile (Fig. 1). As shown in Fig. 1, the k' values of the cations lithium, sodium and potassium showed steady and modest increase with increasing acetonitrile but rose rapidly when acetonitrile increased to 80–90%. Once acetonitrile reached 95%, the k' values increased rapidly for all three cations.

Increasing organic content reduced the ionic strength of the mobile phase, thus causing longer retention of the cations. The dramatic increase of k' values indicated that at very high organic mode (80–95% of acetonitrile), the dominant interaction shifted from ionic to HILIC. Among the cations studied, lithium is the strongest in terms of polarizing ability followed by sodium then potassium based on their charge/radius ratio. HILIC interaction was strongest for lithium resulting in the steepest slope followed by sodium and then potassium.

It is noted that chloride anion showed a partially reciprocal retention trend compared with the cations (Fig. 1). When mobile phase contained less than 50% acetonitrile, chloride did not elute indicating strong anion exchange interaction. As acetonitrile increased from 50% to 90%, the retention time of chloride steadily decreased and behaved differently than the cations. Since higher acetonitrile resulted in weaker mobile phase ionic strength, Cl^- anion was expected to be retained longer. However, with higher organic content, the weak anion exchange domain on the column also became less ionized that would weaken the AEX interaction thus anion retention. In this case, the effect from AEX weakening exceeded that of ionic strength weakening of the mobile phase and resulted in a decrease of Cl^- retention. On the other hand, ionization of the strong cation exchange domain was less affected by acetonitrile change, so the cation elution was still mainly controlled by ionic strength of the mobile phase. As seen in Fig. 1, when acetonitrile increased to 95%, the retention trend of chloride reversed dramatically and behaved similarly as cations with its k' value increased from 13 to 16. The study demonstrated that the dominant retention mechanism may change in mixed mode column due to organic/ionic variation of the mobile phase. HILIC became the dominant interaction when mobile phase contained large percentage of organic phase and at this level, ion exchange became less effective for both cation and anion.

3.2. HILIC/hydrophobic interactions in API matrix separation

Pharmaceutical compounds typically have certain hydrophilicity and hydrophobicity in order to be bioavailable as well as bind to the target. We studied three proprietary small molecule drugs and two commercial drugs, naproxen sodium and tamoxifen as they represented the typical pharmaceutical compounds with a range of chemical properties. GB1, GB2 and tamoxifen are basic drugs, GN1 is a neutral drug, naproxen is an acidic drug. Using similar conditions described in 3.1, the hydrophilic/hydrophobic behaviors of these compounds were tested. As shown in Fig. 2, GB1, GB2, naproxen and tamoxifen all have "U" shaped elution pattern demonstrating coexistence of both hydrophobic and HILIC interactions as acetonitrile level changed from low to high. At lower acetonitrile level, the mobile phase was more polar and the compounds were retained by hydrophobic interaction. A valley bottom was seen around 80% of acetonitrile where the compounds were retained in minimum. As acetonitrile increased from 80% to 95%, the retention time turned upward for all compounds except for the neutral compound GN1 indicating that HILIC interaction became active. At 95% acetonitrile, the k' values for all four basic and acid compounds increased by ~2 folds ($k' = 1.5–3.5$) suggesting that HILIC became dominant retention mechanism. However, compared with the cations and anions, HILIC effect was relatively limited on the retention of API's.

Fig. 2 shows that the neutral compound GN1 was strongly retained by hydrophobic interaction ($k' = 9.3$) at 20% acetonitrile. As acetonitrile increased, the retention time drastically decreased and the compound became unretained ($k' < 1$) between 40% and 95% of acetonitrile. This indicates that HILIC has little effect even at high organic level and the lack of HILIC interaction was likely due to the compound's neutral nature.

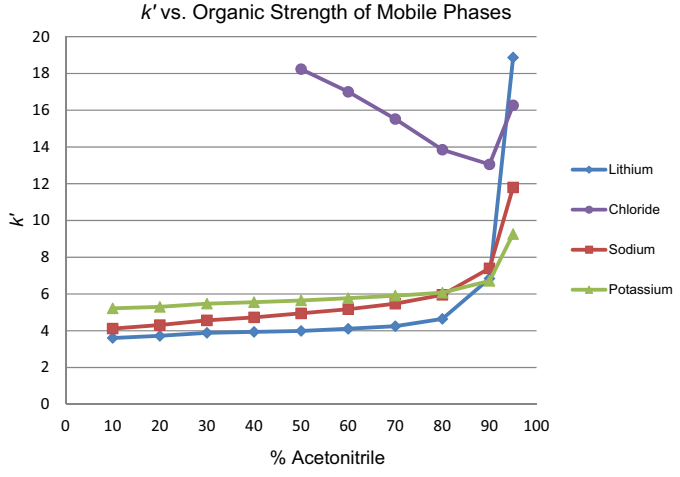

Fig. 1. Correlation of the retention factor k' of ions vs. mobile phase acetonitrile strength. Mobile phase: 5 mM ammonium formate (pH 4.0) in 10–95% acetonitrile. Refer to Section 2.3 for other chromatographic conditions.

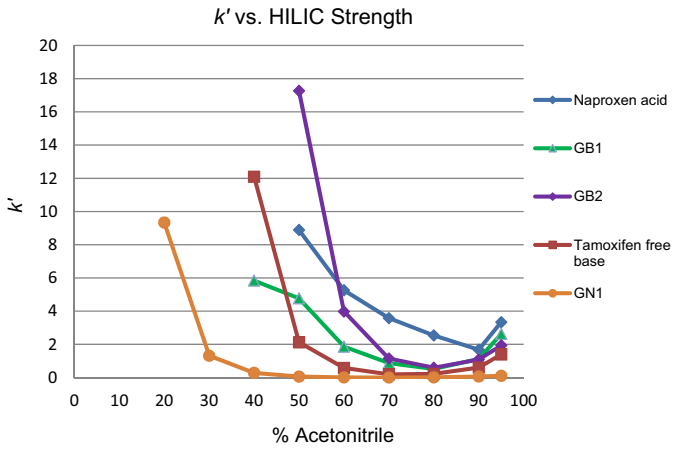

Fig. 2. Correlation of retention factor k' of API compounds vs. acetonitrile strength. Mobile phase: 5 mM ammonium formate (pH 4.0) in 20–95% acetonitrile. Refer to Section 2.3 for other chromatographic conditions.

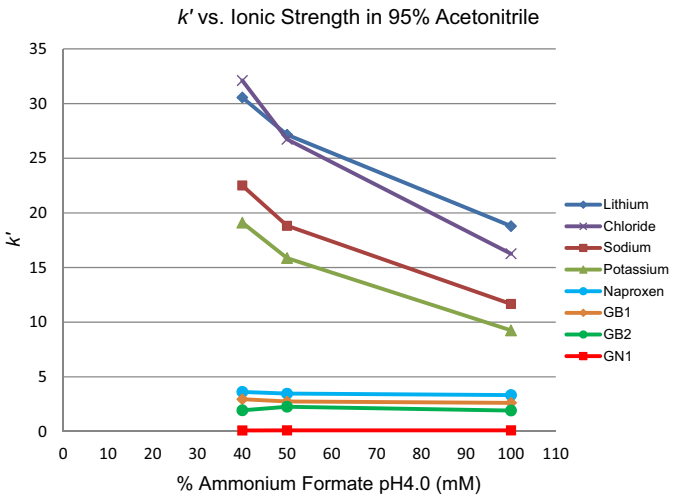

Fig. 3. Correlation of retention factor k' vs. the ionic concentration under HILIC condition. Mobile phase: 95% acetonitrile and 5% ammonium formate (pH 4.0) at 40 mM, 50 mM and 100 mM. Refer to Section 2.3 for other chromatographic conditions.

3.3. Retention behavior with ionic strength and pH under HILIC mode

The correlation between retention of cations and anions vs. different buffer strengths or pH under HILIC mode was studied. Using isocratic mobile phase containing 95% of acetonitrile with 5% ammonium formate either with ionic concentration range of 40–100 mM (pH = 4.0) or pH range of 3.5–4.5 (50 mM).

Fig. 3 shows that the retention factor k' of all cations and anions were strongly affected by the ionic strength of the mobile phase. Although HILIC was the dominant interaction at high organic level as shown in Fig. 1, ion exchange simultaneously existed. With higher ionic concentration (100 mM), retention due to HILIC was reduced for all the ions. The API's were not affected by ionic strength and confirmed that they were not involved in ion exchange activities.

Fig. 4 shows that pH had little effect on retention of all API compounds and very small effect on the retention of ions. Since HILIC was the dominant interaction at 95% of acetonitrile, this indicates that HILIC retention force is not significantly affected by pH.

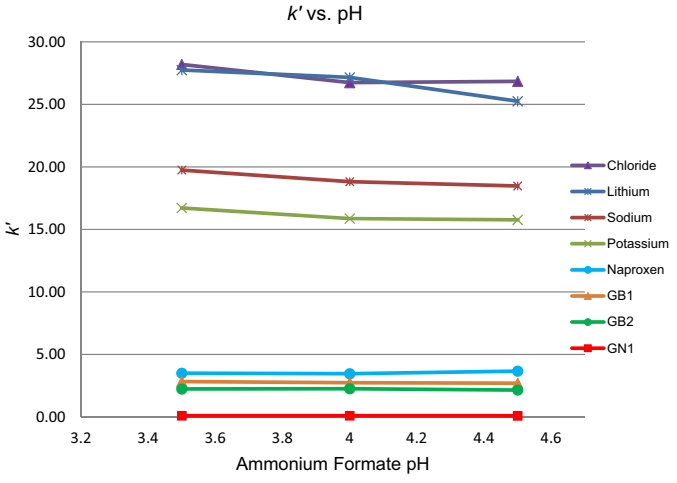

Fig. 4. Correlation of retention factor k' vs. buffer pH. Mobile phase: 95% acetonitrile and 5% ammonium formate (50 mM) at pH 3.5, 4.0 and 4.5. Refer to Section 2.3 for other chromatographic conditions.

Table 1
Chromatographic condition for lithium analysis.

Column	Trinity P1, 3.0 mm × 50 mm, 3 μm
Flow	0.5 mL/min
Column temperature	25 °C
Autosampler temperature	Ambient
Injection volume	10 μL
Mobile phase A	50 mM ammonium formate, pH 4.0
Mobile phase B	Acetonitrile
Mobile phase C	Deionized water

Gradient	Time	% A	% B	% C
	0	10	75	15
	6	10	50	40
	6.1	90	5	5
	10	90	5	5
	10.1	10	75	15
	15	10	75	15

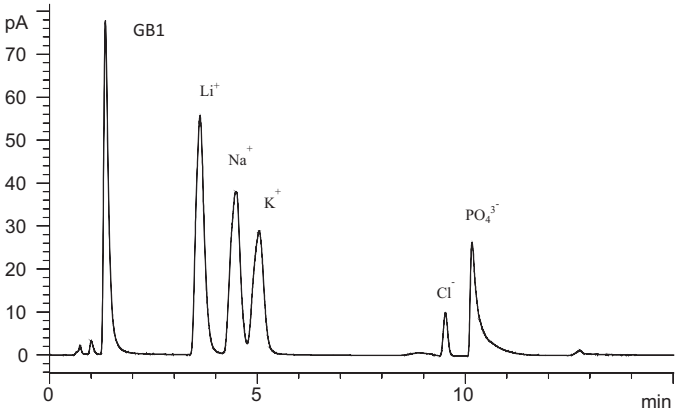

Fig. 5. Chromatogram for the separation of lithium, GB1 drug matrix and other potential ions. with Li 16.1 μg/mL, Na 33.8 μg/mL, K 52.4 μg/mL, Cl 52.1 μg/mL and PO4 138.9 μg/mL. See Table 1 for chromatographic conditions.

3.4. Chromatographic separation space and conditions of lithium analysis

The studies showed a clear separation space where drug matrix, anions and other cations are separated from lithium. Fig. 1 shows that the separation between lithium and other ions occurred in the range of 70–80% acetonitrile. Fig. 2 shows that between 70% and 90% acetonitrile levels, all drug compounds were little or only slightly retained. These revealed that the separation space around 75% acetonitrile gives the best selectivity of lithium among all other cations and compound matrices. For anions Cl^- and PO_4^{3-}, a gradient mobile phase with stronger ionic strength was applied to elute them out.

The final chromatographic condition is listed in Table 1. Fig. 5 shows the chromatogram of the separation of the Li^+, Na^+, K^+, Cl^- and PO_4^{3-} along with API GB1.

Since the API properties may vary, it is possible to fine tune the organic level or ionic gradient to achieve optimal separation of the matrix and interfering ions from lithium. However, it is not recommended to operate at very high organic level as HILIC interaction has strong effect which could cause the ions being retained too strongly and not elute out.

3.5. Method validation

The final method (Table 1) was validated for linearity, sensitivity (LOD, LOQ), accuracy, specificity and precision.

Table 2
Result of method accuracy and precision.

Concentration (μg/mL)	% recovery (n = 6)	% RSD
0.016 (LOQ)	103	7.5
0.032	96	3.2
0.33	97	2.2
1.61	97	1.1

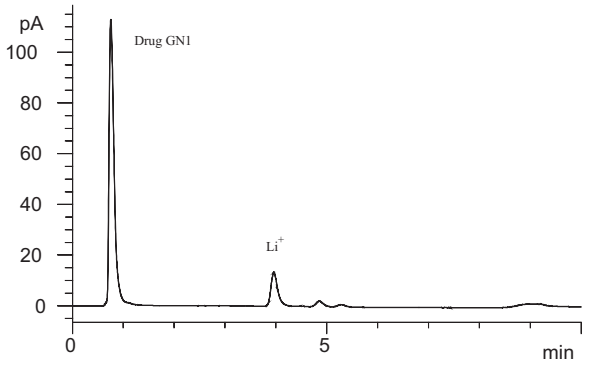

Fig. 6. Chromatogram of lithium accuracy validation in drug matrix GN1. Concentration of Li^+ is 1.6 μg/mL.

3.5.1. Linearity and range

Linearity of the method was evaluated by analyzing the standard solutions in a serial dilution of the stock standard. The CAD area response (y) of lithium vs. concentration (x) is linear in the range of 0.0168–1.681 μg/mL with $y = 81.878x + 1.7071$ and $R^2 = 0.9992$.

3.5.2. Accuracy and precision

Accuracy was tested at LOQ and three higher concentration levels by spiking the lithium standards into six replicates of GN1. The result is shown in Table 2 with the recovery ranging between 96% and 103% for all levels and %RSD between 1.1% and 3.2% for the range of 0.032–1.61 μg/mL and <10% at LOQ level. Fig. 6 shows the chromatogram of an accuracy sample.

3.5.3. Sensitivity

The sensitivity of lithium was tested in the standard solution without sample matrix and spiked into sample matrix. The sample solution was prepared by spiking the lithium standard into drug substance GN1. The results for the LOD and LOQ are listed in Tables 3 and 4. The LOD was determined to be 0.08 ng (8 ppb) in both standard and sample solutions with 10 μL injection volume. As the injection volume was increased to 20 μL and 50 μL or 100 μL, LOD further improved respectively to 0.04 ng (4 ppb) and 0.02 ng (2 ppb). The LOQ was determined to be 0.16 ng (16 ppb) in both standard and sample solutions with injection volume of 10 or 20 μL. When the injection volume increased to 50 μL or 100 μL, the LOQ could be achieved at 0.08 ng (8 ppb). However it was noted that as the injection volume increased, the peak sometimes became broader or split. Therefore it was not always desirable to increase the injection volume in order to achieve better LOQ. The detection and quantitation sensitivity were similar in both standard and sample solutions confirming that there were no interference from the matrix. Comparing with the sensitivity by ICP-AES, this method yielded comparable LOD and LOQ for lithium analysis with the advantages of no pre-sample treatment and elemental/matrix interferences. Lithium ion was found to have exceptionally high detection sensitivity by CAD relative to sodium ion which has been reported as having the lowest LOD of 0.5 ng [30]. The 25-fold sensitivity difference is probably due to the fact that lithium has least weight and largest charge/radius ratio among all metal ions.

Table 3
Lithium detection limit results.

Injection volume	10 μL	20 μL	50 μL	100 μL
Standard solution	0.08 ng (8 ppb)	0.04 ng (4 ppb)	0.02 ng (2 ppb)	0.02 ng (2 ppb)
Sample solution in drug GN1 sample matrix	0.08 ng (8 ppb)	0.04 ng (4 ppb)	0.02 ng (2 ppb)	0.02 ng (2 ppb)

Table 4
Lithium quantitation limit results.

Injection volume	10 μL	20 μL	50 μL	100 μL
Standard Solution	0.16 ng (16 ppb)	0.16 ng (16 ppb)	0.08 ng (8 ppb)	0.08 ng (8 ppb)
Sample solution in drug GN1 sample matrix	0.16 ng (16 ppb)	0.16 ng (16 ppb)	0.08 ng (8 ppb)	0.08 ng (8 ppb)

3.5.4. Specificity

The method is specific for lithium analysis since the elemental and matrix interference were separated by the chromatography. Recovery of lithium in both standard and sample solutions demonstrated excellent accuracy.

4. Conclusion

A universal method for lithium analysis was developed using mixed mode hydrophobic/ion exchange mechanisms in reversed phase mobile phase. A CAD detector was used for the detection and quantitation of lithium ion. The multimodal mechanisms allowed separation of lithium from the interfering matrix compound and other ions, therefore provided outstanding selectivity and accuracy results. Compared with the ICP-AES spectrometry technique, the method presented excellent sensitivity for the determination of lithium ion with similar levels for LOD and LOQ. Another advantage of the method is the minimum sample treatment required which provides high efficiency throughput. The method may not be the fastest method for lithium analysis for a single run, but it can be automated for large amount of samples in a sequence. The study demonstrates that using mixed mode HPLC chromatography is a simple and sensitive approach to eliminate interferences from coexisting ions and matrix. The method has been validated for pharmaceutical samples and can potentially be expanded for lithium analysis in biological, environmental and food samples.

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